Syntheses of Macrocyclic Enzyme Models. Part 6.[1] Preparation and Guest-Binding Behaviour of Octopus Cyclophanes

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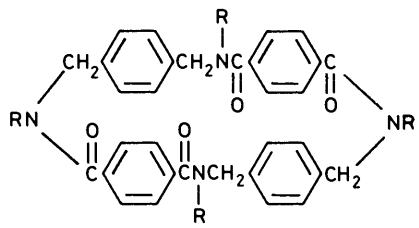
The following octopus cyclophanes constructed with a rigid macrocyclic skeleton and eight flexible hydrocarbon chains were prepared: *N,N',N'',N'''*-tetrakis(2-{*N*-[1-(*N,N*-ditetradecylcarbamoyl)-5-ammoniopentyl]carbamoyl}ethyl)-3,10,21,28-tetraoxo-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane tetrachloride [APC(C_2Lys2C_{14})$_4$] and *N,N',N'',N'''*-tetrakis[2-(*N*-{1-(*N,N*-ditetradecylcarbamoyl)-1-[5-(trimethylammonio)pentanecarboxamido]pentan-5-yl}carbamoyl)ethyl]-3,10,21,28-tetraoxo-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane tetrabromide {APC[C_2Lys(C_5N^+)2C_{14}]$_4$}. These host molecules provide cavities that are deep and hydrophobic enough to incorporate hydrophobic guests of various bulkiness through an induced-fit mechanism originating from the flexible character of the alkyl branches. Both hydrophobic and electrostatic interactions come into effect in the host–guest complexation process, so that the molecular recognition is exercised by the present hosts towards guest molecules. As regards the inclusion equilibrium between APC[C_2Lys(C_5N^+)2C_{14}]$_4$ and pyrene, formation of both 1 : 2 and 1 : 1 (host : guest) complexes was remarkably favoured. The hydrophobic cage provided by the octopus cyclophane is highly apolar and acts to repress the molecular motion of guests; this was confirmed by fluorescence and fluorescence polarization spectroscopy, respectively. Both 2-azidobiphenyl and pyrene were simultaneously incorporated into the cyclophane cage as evidenced by kinetic analysis, and the pyrene-sensitized photolysis of the former species was enhanced under such conditions. The results imply that the octopus cyclophanes can be utilized as effective apoenzyme models for simulation of enzymatic functions.

Enzymes are ingeniously designed natural hosts demonstrating distinct substrate discrimination. Although such host–guest interactions have been basically explained by the lock-and-key concept, the importance of the induced-fit type recognition has often been emphasized for some enzymatic reactions.[2] In recent years, macrocyclic molecules having a hydrophobic internal cavity, such as cyclophanes and cyclodextrins, have been widely employed as simplified models for simulation of enzymatic functions.[3] The rigid macrocyclic skeletons of such molecules are generally used to aim at the regiospecific host–guest interaction. We have developed so-called octopus-like cyclophanes which recognize various guests through the induced-fit mechanism. This interaction mode originates from the flexible character of four alkyl branches introduced into a rigid macrocyclic skeleton.[4–6] In aqueous media, each of these octopus-like cyclophanes can provide a relatively large hydrophobic binding site constructed with a rigid macrocyclic skeleton and flexible hydrocarbon chains, and hydrophobic guest molecules of various bulkiness are effectively incorporated into the hosts primarily through hydrophobic interactions. In addition, the guest recognition through electrostatic and charge transfer interactions becomes effective by introduction of additional functional sites into the host. We have extended the study on cyclophanes having induced-fit binding behaviour towards various guest molecules and have prepared real octopus cyclophanes having eight arms of hydrocarbon character.[7] The guest-binding abilities of the host molecules and the microenvironmental properties provided by their hydrophobic cavities were characterized in this work by means of electronic absorption, fluorescence, and fluorescence polarization spectroscopy.

Results and Discussion

Preparation and Properties.—In this work, we designed two octopus cyclophanes bearing eight hydrocarbon chains, one having four amino groups and the other possessing four quaternary ammonium entities as the polar segments;



R = $(CH_2)_nCO_2H$: APC(C_nCO_2H)$_4$ (n = 2, 10) **(I)**

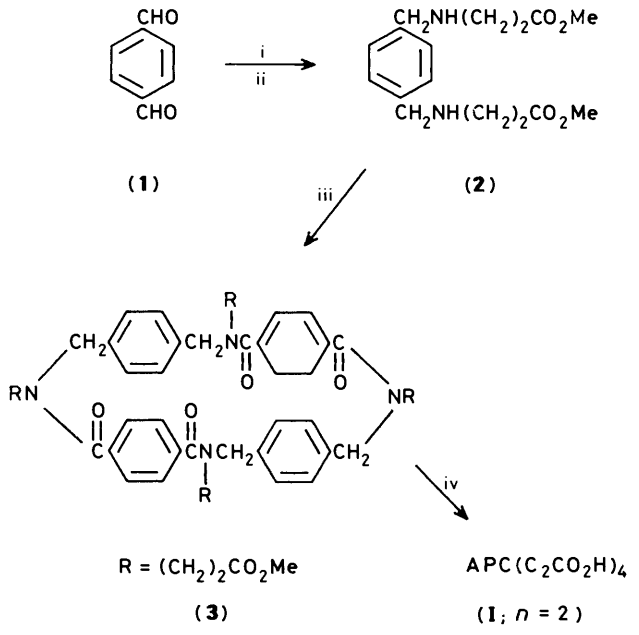
R = $(CH_2)_{10}N^+Me_3\ I^-$: APC($C_{10}N^+$)$_4$ **(II)**

R = $(CH_2)_2CNHCHCN[(CH_2)_{13}Me]_2$ (with $(CH_2)_4N^+H_3\ Cl^-$) : APC(C_2Lys2C_{14})$_4$ **(III)**

R = $(CH_2)_2CNH(CH_2)_4CHCN[(CH_2)_{13}Me]_2$ (with $NHC(CH_2)_5N^+Me_3\ Br^-$) :

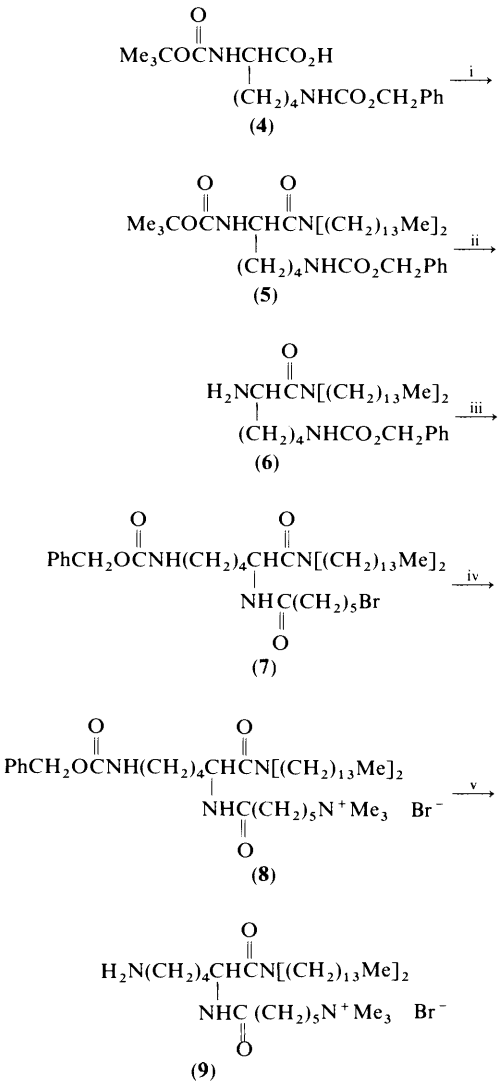
APC[C_2Lys(C_5N^+)2C_{14}]$_4$ **(IV)**

N,N',N'',N'''-tetrakis(2-{*N*-[1-(*N,N*-ditetradecylcarbamoyl)-5-ammoniopentyl]carbamoyl}ethyl)-3,10,21,28-tetraoxo-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane tetrachloride [APC(C_2Lys2C_{14})$_4$] **(III)** and *N,N',N'',N'''*-tetrakis[2-(*N*-{1-(*N,N*-ditetradecylcarbamoyl)-1-[5-(trimethylammonio)pentanecarboxamido]pentan-5-yl}carbamoyl)ethyl]-3,10,21,28-



Scheme 1. *Reagents:* i, $H_2N(CH_2)_2CO_2Me$; ii, $H_2/PdCl_2$–C; iii, *p*-$ClOCC_6H_4COCl$; iv, OH^-

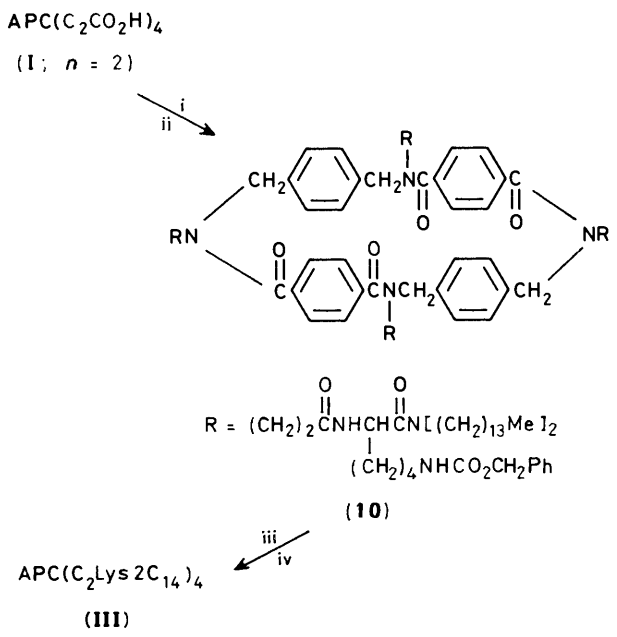
tetraoxo-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane tetrabromide {$APC[C_2Lys(C_5N^+)2C_{14}]_4$} (**IV**), respectively. The synthetic steps are shown in Schemes 1—3. *N,N′,N″,N‴*-Tetrakis(2-carboxyethyl)-3,10,21,28-tetraoxo-2,11,20,29-tetraaza[3.3.3.3]paracyclophane [$APC(C_2CO_2H)_4$] (**I**; $n = 2$), which is constructed with a rigid macrocyclic skeleton and four short side chains, was chosen as the basic building block for both of the octopus cyclophanes. This compound was prepared by condensation of terephthaloyl dichloride with *N,N′*-bis(2-methoxycarbonylethyl)-*p*-xylylenediamine (**2**) under high dilution conditions and subsequent alkaline hydrolysis in a manner similar to that reported for the synthesis of *N,N′,N″,N‴*-tetrakis(10-carboxydecyl)-3,10,21,28-tetraoxo-2,11,20,29-tetraaza[3.3.3.3]paracyclophane [$APC(C_{10}CO_2H)_4$] (**I**; $n = 10$)[4] (Scheme 1). The other structural components, flexible hydrocarbon segments having a charged portion, were prepared according to Scheme 2. *N,N*-Ditetradecyl-N^{α}-t-butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysinamide (**5**) was obtained by condensation of ditetradecylamine with N^{α}-t-butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysine in the presence of dicyclohexylcarbodi-imide (DCC). Removal of the t-butoxycarbonyl group of (**5**) by treatment with an excess of formic acid gave *N,N*-ditetradecyl-N^{ε}-benzyloxycarbonyl-L-lysinamide (**6**). This amine component was coupled with 6-bromohexanoyl chloride, and the bromo group was replaced with the trimethylammonium group to afford *N,N*-ditetradecyl-N^{α}-[6-(trimethylammonio)hexanoyl]-N^{ε}-benzyloxycarbonyl-L-lysinamide bromide (**8**). The benzyloxycarbonyl group of compound (**8**) was removed by hydrogenation with Pd–C as catalyst to give *N,N*-ditetradecyl-N^{α}-[6-(trimethylammonio)hexanoyl]-L-lysinamide bromide (**9**). As regards the synthesis of (**III**), the tetra(acid chloride) form of (**I**; $n = 2$) underwent reaction with compound (**6**) to give the precursor, *N,N′,N″,N‴*-tetrakis[2-(*N*-{1-(*N,N*-ditetradecylcarbamoyl)-5-[*N*-(benzyloxycarbonyl)-aminopentyl]}carbamoyl)ethyl]-3,10,21,28-tetraoxo-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (**10**). Subsequently, the benzyloxycarbonyl group of (**10**) was removed with hydrogen bromide in trifluoroacetic acid, and the product was isolated as the hydrochloride salt (Scheme 3). The macrocycle



Scheme 2. *Reagents:* i, $HN[(CH_2)_{13}Me]_2$, DCC; ii, HCO_2H; iii, $Br(CH_2)_5COCl$; iv, NMe_3; v, H_2/Pd–C

(**III**) thus obtained is soluble in acidic aqueous media. Meanwhile, (**IV**) was obtained by condensation of the acid chloride form of (**I**; $n = 2$) with (**9**) and was found to be soluble in aqueous media over the whole pH range.

The CPK molecular model of (**III**) under the configurational situation that allows the most efficient association of its eight hydrocarbon chains in aqueous media is shown in Figure 1 along with its schematic representation. The size of the hydrophobic cavity is subject to wide variation due to the flexible character of the hydrocarbon chains, and the cavity size is likely to be controlled by the bulkiness of incorporated guest molecules. In addition, it is notable that the cavity interior is shielded from the bulk aqueous phase much more efficiently than those of the octopus-like cyclophanes[4–6,8] and other cyclophanes reported so far.[3,9] Consequently, the effective desolvation of incorporated guest molecules can be expected. In the light of the CPK molecular model, compound (**IV**) may provide a hydrophobic interior similar to that of (**III**) with respect to the cavity size and the shielding effect, although the connector portion interposed between the macrocyclic skeleton and the double-chain segment is somewhat longer in the former than in the latter.



Scheme 3. *Reagents:* i, $SOCl_2$; ii, (**6**); iii, HBr/CF_3CO_2H; iv, ion exchange

The critical aggregate concentrations (cac) of these octopus cyclophanes were determined in aqueous media by surface tension measurements in a manner similar to that reported previously;[4] 1.0×10^{-4} and 5.0×10^{-4} mol dm^{-3} for (**III**) (at pH 6.0) and (**IV**) (at pH 7.0), respectively. Thus, the cyclophane concentration was maintained in a range below their cac values for all measurements on the host–guest interactions between the octopus cyclophanes and various guest molecules.

Guest-Binding Ability.—The guest-binding behaviour of the octopus cyclophanes, (**III**) and (**IV**), was examined by fluorescence and electronic absorption spectroscopy in the following aqueous media at 30 °C; an aqueous 2-morpholinoethanesulphonate (MES) buffer [0.01 mol dm^{-3}, pH 6.0, μ 0.10 (KCl)] containing 5% (v/v) ethanol for (**III**), and an aqueous 2-[4-(2-hydroxyethyl)piperazinyl]ethanesulphonate (HEPES) buffer [0.01 mol dm^{-3}, pH 8.0, μ 0.10 (KCl)] containing 5% (v/v) ethanol for (**IV**). The octopus-like cyclophane, *N*,*N*′,*N*″,*N*‴-tetrakis[10-(trimethylammonio)decyl]-3,10,21,28-tetraoxo-2,11.20.29-tetra-aza[3.3.3.3]paracyclophane tetraiodide [$APC(C_{10}N^+)_4$] (**II**)[5] was used as a reference host, and the following hydrophobic probes were chosen as guests: 8-anilinonaphthalene-1-sulphonate (ANS), 6-*p*-toluidinonaphthalene-2-sulphonate (TNS), 7-hydroxy-8-phenylazonaphthalene-1,3-disulphonate (OG), and pyrenylbutanoate (PB) as anionic ones; pyrene (Py), 2-hydroxy-1-(2-pyridylazo)naphthalene (PAN), and *N*-phenylnaphthyl-1-amine (PNA) as nonionic ones; 1-dimethylaminonaphthalene-5-sulphonamidoethyltrimethylammonium (DASP) and 2-(*p*-dimethylaminostyryl)-1-ethylquinolinium (QR) as cationic ones.

The fluorescence intensities for the anionic and nonionic guest molecules, ANS, TNS, PB, and PNA, increased on addition of the host compounds cited above. The fluorescence spectra of ANS upon addition of (**III**) at various concentrations are shown in Figure 2 as a typical example. The ANS molecule incorporated into the cyclophane exhibited remarkably strong intensity at the lower fluorescence maximum ($\lambda_{max.}$ 461 nm) relative to its emission in water ($\lambda_{max.}$ 515 nm). The binding constants were evaluated on the basis of the Benesi-Hildebrand relationship[10] for the 1:1 host–guest interaction, and good

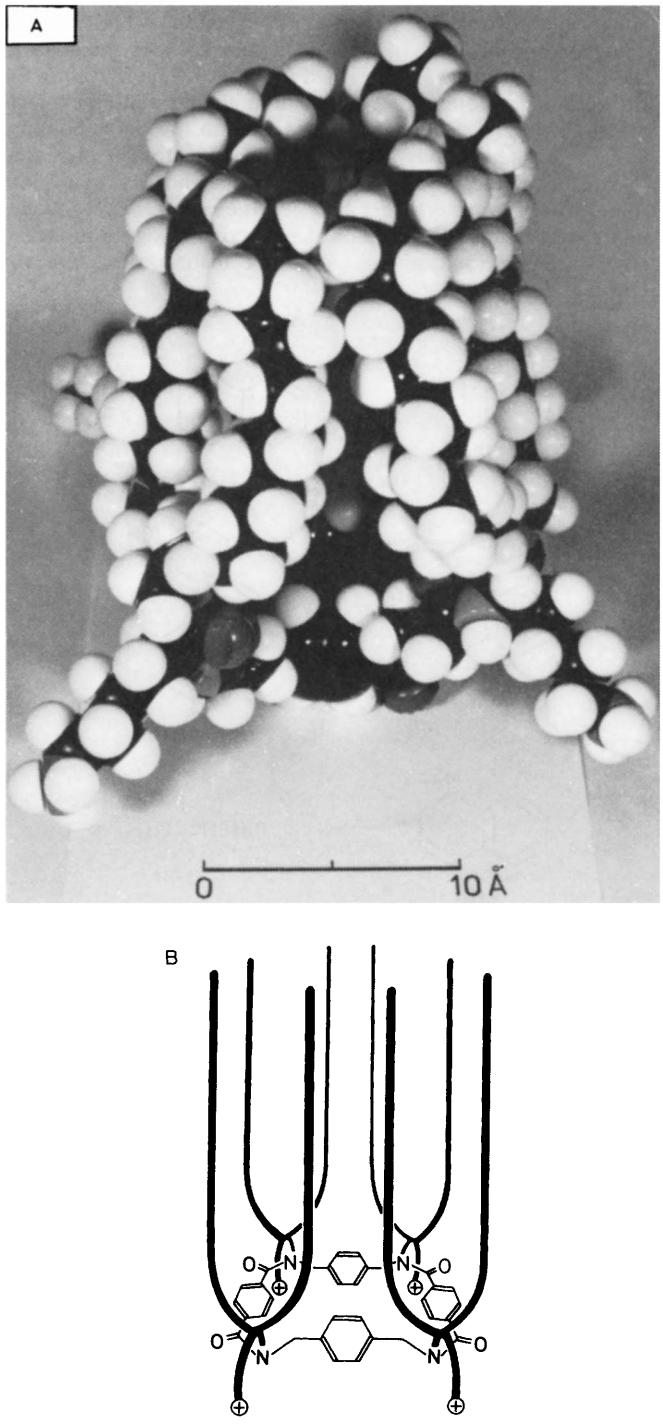
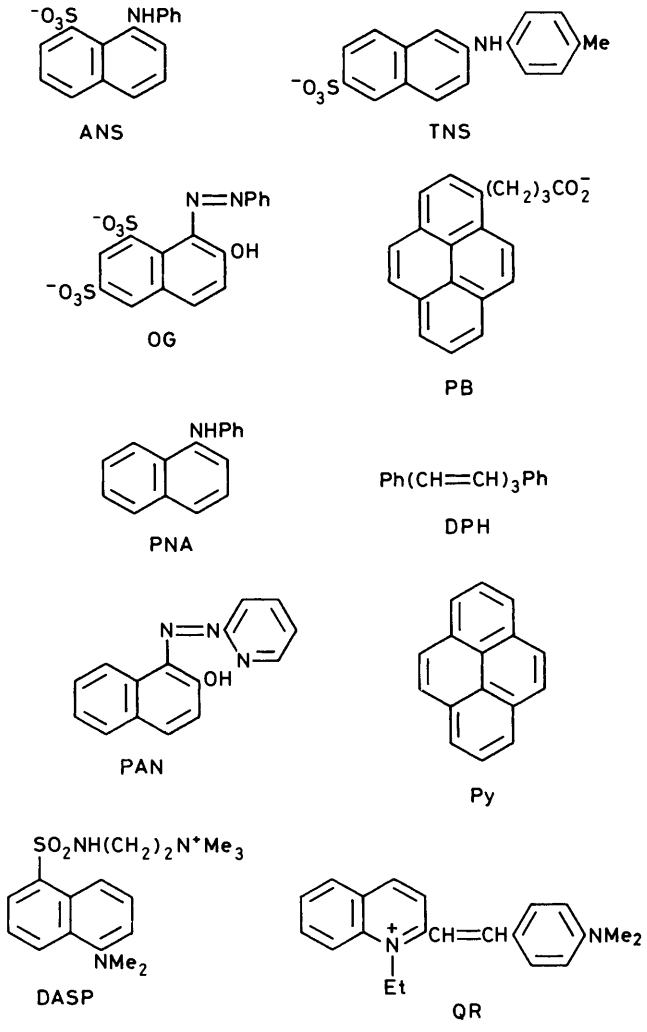


Figure 1. CPK molecular model of $APC(C_2Lys2C_{14})_4$ (**III**), showing the most efficient hydrophobic association of its eight hydrocarbon chains in aqueous media (A), and its schematic representation (B)

linear correlations with respect to double-reciprocal plots of the extent of fluorescence intensity change upon addition of the host (ΔI) against the total concentration of the host molecule ($[H]_0$) [see equation (iv) in the Experimental section] were obtained with the above four guest compounds. On the other hand, addition of each cationic host to the cationic fluorescent guest, DASP, did not result in any spectral change. For the non-fluorescent guests such as OG, PAN, and QR, the host–guest interactions were measured by electronic absorption spectroscopy in a manner similar to that reported previously[4,5] [see

equation (iii) in the Experimental section]. The binding constants for inclusion of these guest molecules by the hosts at the 1:1 molar ratio (K_1) are listed in Table 1. The K_1 values for the octopus cyclophanes with the anionic and nonionic guests are 1—3 orders of magnitude greater than the corresponding values for the octopus-like cyclophane due to the increased hydrophobic effect exercised by the former hosts. In addition, the electrostatic interaction between the octopus cyclophanes and the guest molecules is another effective recognition factor, so that the cationic guests cannot be incorporated into the cationic hosts.



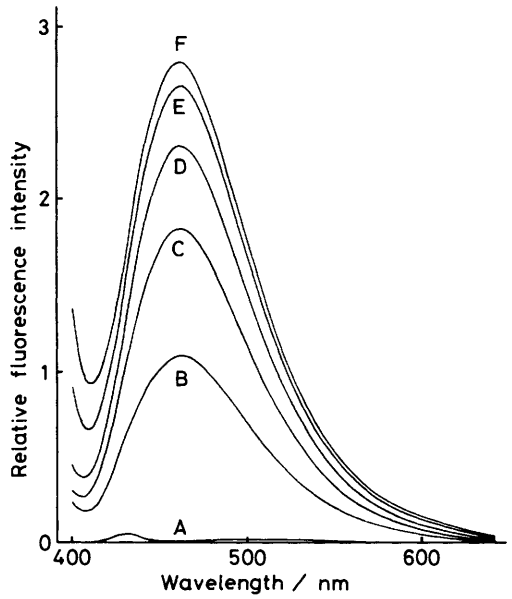


Figure 2. Fluorescence spectra of ANS (1.0×10^{-6} mol dm^{-3}) on addition of APC(C_2Lys2C_{14})$_4$ (**III**) in an aqueous MES buffer (0.01 mol dm^{-3}, pH 6.0, μ 0.10 with KCl) containing 5% (v/v) ethanol at 30 °C; excitation wavelength, 375 nm. Concentrations of (**III**) in mol dm^{-3}: A, 0; B, 2.5×10^{-6}; C, 5.0×10^{-6}; D, 1.0×10^{-5}; E, 2.0×10^{-5}; F, 3.0×10^{-5}. The peak at 432 nm in spectrum A is due to Raman scattering of water

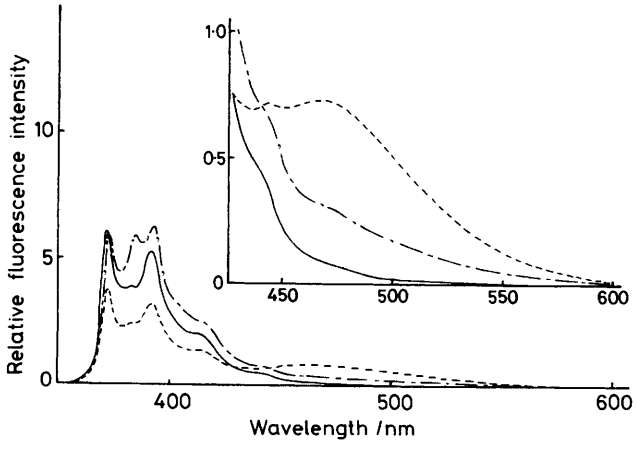


Figure 3. Fluorescence spectra of pyrene (1.0×10^{-6} mol dm^{-3}) upon addition of APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (**IV**) in an aqueous HEPES buffer (0.01 mol dm^{-3}, pH 8.0, μ 0.10 with KCl) containing 0.1% (v/v) ethanol at 30 °C; excitation wavelength, 337 nm. Concentrations of (**IV**) in mol dm^{-3}: ——, 0; – – – –, 1.0×10^{-6}; — — —, 3.1×10^{-5}

Table 1. Binding constants (K_1/dm^3 mol^{-1}) for inclusion of various guest molecules by cyclophanes in aqueous media at 30 °C[a]

Guest	Method[b]	APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (**IV**)[c]	APC(C_2Lys2C_{14})$_4$ (**III**)[d]	APC($C_{10}N^+$)$_4$ (**II**)[d]
ANS	F	2.5×10^5	2.8×10^5[e]	1.1×10^4[e]
TNS	F	4.7×10^5	3.0×10^5[e]	7.5×10^3[e]
PB	F	9.1×10^5		
OG	E		1.4×10^5	5.2×10^2[f]
PNA	F	2.6×10^5	1.3×10^6[e]	4.6×10^3[e]
PAN	E		3.7×10^5	3.5×10^2[f]

[a] Concentrations in mol dm^{-3}: guests, 1.0×10^{-6}; (**II**), 5.0×10^{-5}—3.0×10^{-4}; (**III**) and (**IV**), 5.0×10^{-6}—3.0×10^{-5}. Complex formation was not detected with QR and DASP by electronic absorption and fluorescence spectroscopy respectively. [b] F, Fluorescence spectroscopy; E, electronic absorption spectroscopy. [c] In an aqueous HEPES buffer (0.01 mol dm^{-3}, pH 8.0, and μ 0.10 with KCl) containing 5% (v/v) ethanol. [d] In an aqueous MES buffer (0.01 mol dm^{-3}, pH 6.0, and μ 0.10 with KCl) containing 5% (v/v) ethanol. [e] Ref. 7. [f] Ref. 5.

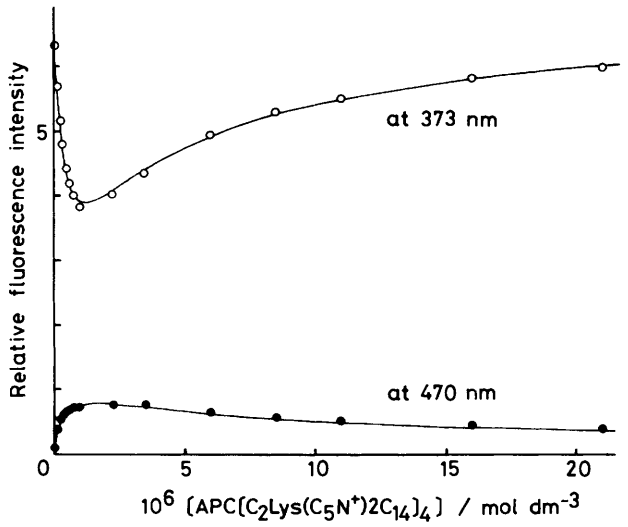


Figure 4. Correlations of intensities of the monomer (○) and excimer (●) of pyrene (1.0×10^{-6} mol dm^{-3}), in an aqueous HEPES buffer (0.01 mol dm^{-3}, pH 8.0, μ 0.10 with KCl) containing 0.1% (v/v) ethanol, with concentration of APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (**IV**) at 30 °C; excitation wavelength, 337 nm. Solid lines refer to the calculated data on the basis of stability constants; $K_1 = 1.2 \times 10^6$ dm^3 mol^{-1}, $K_2 = 2.4 \times 10^6$ dm^3 mol^{-1}

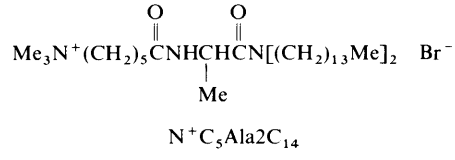
The inclusion behaviour of compound (**IV**) towards pyrene was somewhat different from that towards other guest molecules as clarified by fluorescence spectroscopy. A dilute aqueous solution of pyrene (1.0×10^{-6} mol dm^{-3}) showed emission originating from the monomer species. However, a broad emission band, which is attributed to the pyrene excimer, appeared in a longer wavelength region ($\lambda_{max.}$ 470 nm) with concomitant decrease of the monomer emission upon addition of (**IV**) in a concentration range of 1.25×10^{-7}—1.0×10^{-6} mol dm^{-3} (Figure 3). The excimer and monomer emissions reached a maximum and a minimum intensity, respectively, at the cyclophane concentration of 1.0×10^{-6} mol dm^{-3}, and then the former intensity decreased gradually and the latter intensity increased as the host was added further (Figures 3 and 4). The fluorescence behaviour indicates the formation of two kinds of the inclusion complexes, 1:1 and 1:2 (host:guest) species. Thus, the formation constants for the 1:1 and 1:2 complexes, K_1 and K_2, respectively, were calculated from the fluorescence intensities measured at 373 and 470 nm (Figure 4) on the basis of equilibria shown in Scheme 4 (for details, see the Experimental section). The results are listed in Table 2 together with the corresponding values reported for γ-cyclodextrin (γ-CD) as a host molecule.[11,12] γ-CD Is the only macrocyclic host reported so far as having a hydrophobic cavity large enough to form 1:2 host–guest complexes with aryl compounds.[11–13] Since the hydrophobic cavity of γ-CD is significantly rigid, the formation constant for the 1:2 host–guest complex with pyrene is markedly greater than that for the 1:1 complex. On the other hand, the octopus cyclophane favours the formation of both 1:1 and 1:2 complexes to a remarkable extent due to the induced-fit binding mode. It is notable that formation of the excimer complex of PB was not detected in the presence of (**IV**) under conditions identical with those applied to pyrene. Two molecules of the anionic PB must exercise mutual electrostatic repulsion in the hydrophobic cavity of the host, so that incorporation of the second guest molecule is strongly inhibited.

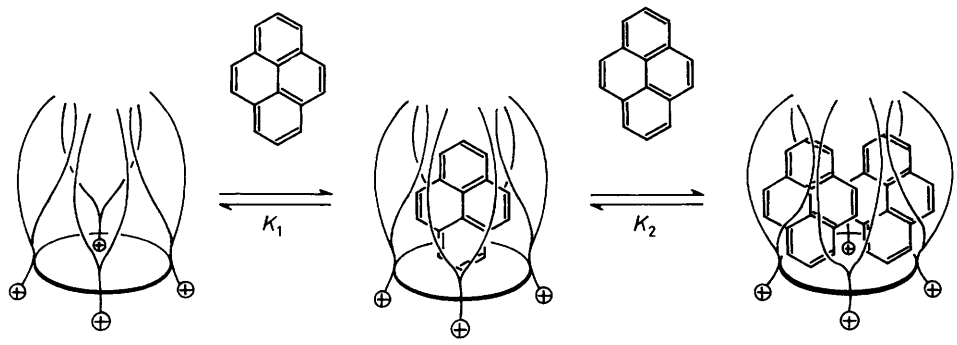
Table 2. Binding constants for inclusion of pyrene

Host	K_1/dm^3 mol^{-1}	K_2/dm^3 mol^{-1}
APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (**IV**)	1.2×10^6	2.4×10^6
γ-Cyclodextrin	20[b]	5×10^6[b]
γ-Cyclodextrin	35[c]	1.9×10^7[c]

[a] Concentrations in mol dm^{-3}: pyrene, 1.0×10^{-6}; (**IV**), 1.25×10^{-7}—3.1×10^{-5}. In an aqueous HEPES buffer (0.01 mol dm^{-3}, pH 8.0, and μ 0.10 with KCl) containing 0.1% (v/v) ethanol at 30 °C. [b] Ref. 11. [c] Ref. 12.

Microenvironmental Properties of Cyclophane Cavity.—The medium polarities of microenvironments around the incorporated guest molecules were evaluated from their fluorescence maxima. In order to obtain the reference data, the fluorescence maxima of ANS were measured in various solvents as shown in Figure 5. The fluorescence maximum was shifted to the lower wavelength region as the solvent polarity decreased. The microenvironments around the guest incorporated into APC-(C_2Lys2C_{14})$_4$ (**III**) and APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (**IV**) are equivalent to those provided by pyridine [E_T(30),[14] 40.2 kcal mol^{-1}] and acetone [E_T(30), 42.2 kcal mol^{-1}], respectively. The octopus cyclophanes provide less polar microenvironments for ANS relative to the octopus-like cyclophane, APC($C_{10}N^+$)$_4$ (**II**), (Figure 5 and Table 3), the hexadecyltrimethylammonium bromide (CTAB) micelle [E_T(30), 56.5 kcal mol^{-1}], and the multiwalled bilayer membrane formed with *N*,*N*-ditetradecyl-*N*$^{\alpha}$-[6-(trimethylammonio)hexanoyl]-L-alaninamide bromide [N^+C_5Ala2C_{14}] [15] [E_T(30), 54 kcal mol^{-1}]. For the nonionic





Scheme 4.

Table 3. Microenvironmental polarity parameters [$E_T(30)^a$/kcal mol^{-1}] for guests incorporated into cyclophanes in aqueous mediat at 30 °C[b]

Guest	APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (IV)	APC(C_2Lys2C_{14})$_4$ (III)[c]	APC($C_{10}N^+$)$_4$ (II)[c]
ANS	42 (375, 462)	40 (375, 461)	55 (375, 481)
TNS	52 (323, 427)	52 (323, 425)	55 (323, 440)
PNA	34 (345, 406)	38 (345, 410)	62 (332, 455)

[a] Ref. 14; 1 kcal = 4.184 kJ. [b] Excitation and emission maxima (in nm) are given in parentheses, in this sequence. Concentrations in mol dm^{-3}: guests, 1.0×10^{-6}; (**II**), 3.0×10^{-4}; (**III**) and (**IV**), 3.0×10^{-5}. Medium conditions are identical with those given in Table 1. [c] Ref. 7.

Table 4. Steady-state fluorescence polarization (P) for guests incorporated into cyclophanes in aqueous media at 30 °C[a]

Guest	APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (IV)	APC(C_2Lys2C_{14})$_4$ (III)[b]	APC($C_{10}N^+$)$_4$ (II)
ANS	0.33	0.29	
TNS	0.31	0.31	
PNA	0.25	0.21	0.058
DPH	0.30	0.29	

[a] Concentrations in mol dm^{-3}: ANS, TNS, and PNA, 1.0×10^{-6}; DPH, 1.0×10^{-7}; (**II**), 3.0×10^{-4}; (**III**) and (**IV**), 3.0×10^{-5}. Medium conditions are identical with those given in Table 1. [b] Ref. 7.

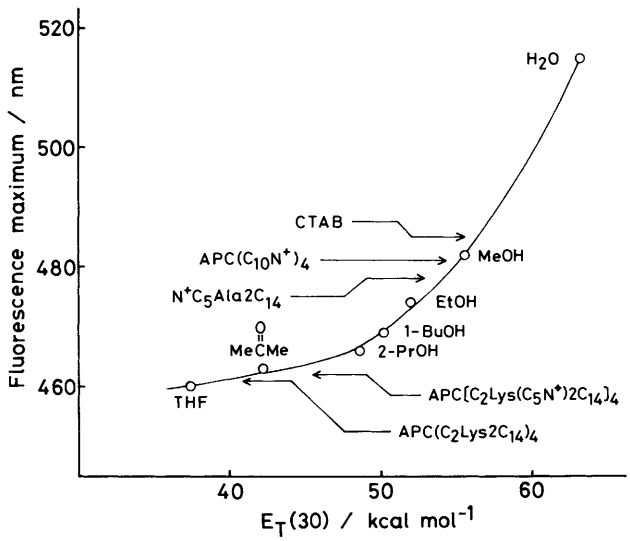


Figure 5. Solvent effect on fluorescence of ANS (1.0×10^{-6} mol dm^{-3}). Concentrations of cyclophanes and medium conditions are given in Tables 3 and 1, respectively

PNA having a molecular shape similar to that of ANS, the octopus cyclophanes provide slightly more apolar microenvironments, presumably due to the electrostatic neutrality of the former guest (Table 3). On the other hand, a guest molecule having a somewhat elongated structure, *i.e.*, TNS, is placed in more polar microenvironments constructed with the octopus cyclophanes (Table 3).

Kalyanasundaram and Thomas reported that the fluorescence intensities for various vibronic fine structures in the pyrene monomer fluorescence showed strong solvent dependence, and that the relative intensity of peak III at 383.03 nm to peak I at 372.51 nm (the III/I ratio) was useful to discuss the environmental effects: the III/I ratios in water, simple polar solvents, micellar systems, aromatic solvents, and hydrocarbons are 0.63, 0.50—0.80, 0.70—1.00, 0.80—1.00, and 1.65—1.75, respectively.[16] From the spectra shown in Figure 3, the III/I ratio for pyrene incorporated into (**IV**) is 0.98, suggesting that a tiny amount of water penetrates into the apolar cavity of the host molecule. These results are in good agreement with the view predicted on the basis of the corresponding CPK molecular models mentioned above.

Relatively large fluorescence polarization values (P 0.2—0.3) were obtained for probes, such as ANS, TNS, PNA, and 1,6-diphenylhexa-1,3,5-triene (DPH), incorporated into the octopus cyclophanes (Table 4). The P value is subjected to change by the fluorescence lifetime (τ) and the relaxation time of rotation (ρ) of a probe[17] [see equation (ii) in the Experimental section]. Since the τ value undergoes variation commensurate to the fluorescence intensity and increases along with a decrease in medium polarity, the relative magnitude of the microscopic viscosity, which is reflected in the ρ value, can be evaluated by comparing the P value in the cyclophane system with that in homogeneous media showing identical fluorescence intensity: the P values in the corresponding homogeneous solutions are much smaller ($P \leqq 0.03$).[7] Thus, the large P values observed in the presence of the hosts primarily reflect high microscopic viscosity in the hydrophobic cavities of the octopus cyclophanes.*

The Hydrophobic Cage as a Reaction Site.—In order to characterize the hydrophobic cavity of the octopus cyclophane as a reaction site, we studied the photochemical reaction of 2-azidobiphenyl in the presence and absence of APC[C_2Lys-(C_5N^+)2C_{14}]$_4$ (**IV**) in aqueous media at 20 °C under anaerobic conditions. It has been reported that direct photo-excitation of 2-azidobiphenyl at 10^{-2} mol dm^{-3} resulted in predominant formation of carbazole along with a low yield of 2-azobiphenyl.[18] At a lower concentration of 2-azidobiphenyl employed in this study (5.0×10^{-5} mol dm^{-3}), carbazole was the only product; confirmed by electronic absorption spectroscopy

* Under the conditions indicated in Table 4, the fluorescence intensity of each guest molecule was drastically enhanced when it was incorporated into (**III**) and (**IV**), and the extent of complexation is *ca.* 90% as evaluated by the aid of the K_1 values listed in Table 1. On this basis, we can obtain the true P values for the incorporated guest molecules. However, the complexation of PNA with (**II**) is 58% under the conditions given in Table 4. In this case, the fluorescence intensity originated from the free PNA can not be neglected, and the true P value must be somewhat larger than 0.058.

Table 5. Reactivity of 2-azidobiphenyl (5.0×10^{-5} mol dm^{-3}) in 4% (v/v) ethanol–water at 20 °C under photochemical conditions

APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (**IV**)/10^{-5} mol dm^{-3}	Pyrene/ 10^{-5} mol dm^{-3}	$10^4 k_{obs}$/s^{-1}	k_{rel}
10	5.0	23	12
5.0	2.5	12	6.3
5.0	0	2.0	1.1
0	5.0	4.2[a]	1.8
0	0	1.9 (2.3[a])	1

[a] In 50% (v/v) ethanol–water.

and h.p.l.c. analysis. The observed rate constants for carbazole formation in the presence and absence of the octopus cyclophane and pyrene as a sensitizer[18] are listed in Table 5. Although the reaction rate was somewhat enhanced in the presence of pyrene (5.0×10^{-5} mol dm^{-3}) in a homogeneous aqueous solution, addition of the octopus cyclophane to this system resulted in significant rate enhancement. Since the reactivity was not affected by the presence of the octopus cyclophane alone, such rate enhancement must arise from efficient formation of the ternary complex composed of the octopus cyclophane, 2-azidobiphenyl, and pyrene, as schematically shown in Figure 6.

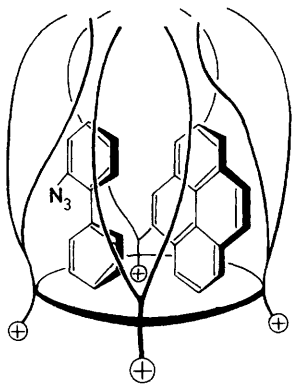


Figure 6. Schematic representation of the reactive ternary complex composed of APC[C_2Lys(C_5N^+)2C_{14}]$_4$ (**IV**), 2-azidobiphenyl, and pyrene molecules

The results imply that the octopus cyclophane can be utilized as a novel apoenzyme model. As one of our approaches along this theory, we have recently constituted an artificial holoenzyme composed of compound (**IV**) and a hydrophobic vitamin B_{12} derivative and demonstrated that such a host–guest complex acted as an effective model for functional simulation of the vitamin B_{12}-dependent methylmalonyl-CoA mutase.[19]

In conclusion, the sterically flexible three-dimensional cavity constructed with a rigid macrocyclic skeleton and eight hydrocarbon chains was characterized here as a deep and efficient binding site for guest molecules of a variety of bulkiness. The molecular recognition primarily originating from the hydrophobic effect is further advanced by an additional electrostatic interaction. In addition, the hydrophobic cage provided by the octopus cyclophane is highly apolar and acts to repress the molecular motion of guest molecules. These characteristic binding capabilities of the host molecules are caused by the induced-fit type inclusion mode, and formation of both 1:1 and 1:2 host–guest complexes are favoured as far as the electrostatic repulsion between guest molecules is not operative in the cyclophane cavity. There is thus scope for the utilization of the octopus cyclophane as an apoenzyme model which simulates various enzymatic functions.

Experimental

Materials.—The following compounds were obtained from commercial sources as guaranteed reagents and used without further purification: magnesium bis(8-anilinonaphthalene-1-sulphonate) [$Mg(ANS)_2$], potassium 6-*p*-toluidinonaphthalene-2-sulphonate [K(TNS)], 1,6-diphenylhexa-1,3,5-triene (DPH), 1-dimethylaminonaphthalene-5-sulphonamidoethyltrimethylammonium perchlorate [(DASP)ClO_4], Quinaldine Red [2-(*p*-dimethylaminostyryl)-1-ethylquinolinium iodide] [(QR)I], and carbazole (all from Nakarai Chemicals, Kyoto, Japan), Orange G (disodium 7-hydroxy-8-phenylazonaphthalene-1,3-disulphonate) [Na_2(OG); Wako Pure Chemical Industries, Osaka, Japan], pyrenylbutanoic acid [H(PB); Molecular Probes, Inc., Oregon, U.S.A.], and 2-hydroxy-1-(2-pyridylazo)naphthalene (PAN; Dojin Chemical Laboratories, Kumamoto, Japan). *N*-Phenyl-1-naphthylamine (PNA; Tokyo Kasei Kogyo Co., Tokyo, Japan) was recrystallized from methanol–water (4:1 v/v), m.p. 61—62 °C. Pyrene (Nakarai Chemicals) was purified by means of liquid chromatography on a column of silica gel (Wako Gel C-100) with cyclohexane as eluant,[20] m.p. 149—151 °C. 2-Azidobiphenyl was prepared in a manner similar to that reported by Smith and Brown[21] (Found: C, 73.8; H, 4.7; N, 21.5. $C_{12}H_9N_3$ requires C, 73.85; H, 4.65; N, 21.5%). Hexadecyltrimethylammonium bromide (CTAB; Nakarai Chemicals) was recrystallized from ethanol, m.p. 237—239 °C (decomp.). Preparation of *N,N′,N″,N‴*-tetrakis[10-(trimethylammonio)decyl]-3,10,21,28-tetraoxo-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane tetraiodide[5] [APC($C_{10}N^+$)$_4$, **II**] and *N,N*-ditetradecyl-*N*$^{\alpha}$-[6-(trimethylammonio)hexanoyl]-L-alaninamide bromide[15] [N^+C_5Ala2C_{14}] has been reported previously. For instrument details see later.

N,N′-*Bis*(2-*methoxycarbonylethyl*)-p-*xylylenediamine* (**2**).—This material was prepared by a procedure similar to that reported for the synthesis of *N,N′*-bis(10-methoxycarbonyldecyl)-*p*-xylylenediamine:[4] a colourless oil (56%) [Found for the free amine: M^+ (e.i. ionization) 308. $C_{16}H_{24}N_2O_4$ requires *M*, 308. Found for the dihydrochloride salt: C, 50.2; H, 6.95; N, 7.25. $C_{16}H_{24}N_2O_4 \cdot 2HCl$ requires C, 50.4; H, 6.85; N, 6.9%); $\nu_{max.}$(neat) 2 950 (CH) and 1 735 cm^{-1} (C=O); δ_H[60 MHz; $CDCl_3$, standard Me_4Si (used throughout unless otherwise stated)] 2.48 (4 H, m, CH_2CO), 2.84 (4 H, m, $NHCH_2CH_2$), 3.60 (6 H, s, Me), 3.71 (4 H, s, benzyl), and 7.16 (4 H, s, ArH).

N,N′,N″,N‴-*Tetrakis*(2-*methoxycarbonylethyl*)-3,10,21,28-*tetraoxo*-2,11,20,29-*tetra-aza*[3.3.3.3]*paracyclophane* (**3**).—Solutions of terephthaloyl dichloride (1.58 g, 7.8 mmol) and compound (**2**) (2.40 g, 7.8 mmol) in dry benzene (100 ml each) were added dropwise to a refluxing solution of triethylamine (28 ml, 200 mmol) in dry benzene (840 ml) at the same rate with vigorous stirring under nitrogen in 11 h, and the mixture was refluxed with stirring for an additional 3 h. The hot mixture was filtered and the filtrate was evaporated to give a pale yellow solid which was subsequently dissolved in acetone (50 ml). The insoluble material was removed by filtration, the solvent was evaporated under reduced pressure, and the residue was purified by gel filtration chromatography on a column of Toyopearl HW-40 fine with methanol–chloroform (1:1 v/v) as eluant. The residue was dried *in vacuo* to give a white solid (800 mg, 24%), m.p. 270—271 °C [Found: C, 64.95; H, 6.3; N, 6.35; M^+ (e.i.), 876. $C_{48}H_{52}N_4O_{12} \cdot 1/2H_2O$ requires C, 65.05; H, 6.05; N, 6.3%; *M* (without $1/2H_2O$), 876]; $\nu_{max.}$(KBr disc) 2 950 and 2 920 (CH), and 1 735 and 1 635 cm^{-1} (C=O); δ_H(400 MHz; $CDCl_3$)

2.82 (8 H, t, *J* 6.6 Hz, CH_2CH_2CO), 3.70 (12 H, s, Me), 3.80 (8 H, m, CH_2CH_2CO), 4.54 (8 H, s, benzyl), 7.16 (8 H, s, ArH), and 7.16 (8 H, s, ArH); δ_C(100 MHz; $CDCl_3$) 32.0 (CH_2CH_2CO), 42.8 (CH_2CH_2CO), 51.9 (Me), 52.6 ($PhCH_2$), 126.3 (C-14, 15, 17, 18, 32, 33, 35, and 36), 126.6 (C-5, 6, 8, 9, 23, 24, 26, and 27), 136.4 (C-4, 7, 22, and 25), 137.0 (C-13, 16, 31, and 34), 171.0 (PhCO), and 172.3 (CH_2CH_2CO). A molecular weight determined by osmometry in chloroform was consistent with that of the 2:2 adduct.

N,N′,N″,N‴-*Tetrakis*(2-*carboxyethyl*)-3,10,21,28-*tetraoxo*-2,11,20,29-*tetra*-*aza*[3.3.3.3]*paracyclophane* [$APC(C_2CO_2H)_4$] (**I**; n = 2).—A mixture of compound (**3**) (400 mg, 0.46 mmol) and aqueous sodium hydroxide (4%; 4 ml) in methanol (40 ml) was refluxed for 20 h and cooled to room temperature. The solvent was evaporated off and the oily residue was dissolved in water (50 ml). After removal of a small amount of insoluble material by filtration, the aqueous solution was adjusted to pH 1 by adding dilute aqueous hydrochloric acid and the solution was left to stand overnight at 5 °C. The precipitates were recovered, washed with water, and purified by gel filtration chromatography on a column of Sephadex LH-20 with methanol as eluant. The residue was dried *in vacuo* to give a white solid (97 mg, 26%), m.p. 302 °C (decomp.) (Found: C, 64.15; H, 5.55; N, 6.8. $C_{44}H_{44}N_4O_{12}$ requires C, 64.4; H, 5.4; N, 6.85%); $\nu_{max.}$(KBr disc) 2 920 and 2 850 (CH), and 1 725 and 1 620 cm^{-1} (C=O); δ_H[400 MHz; $(CD_3)_2SO$] 2.69 (8 H, m, CH_2CH_2CO), 3.83 (8 H, m, CH_2CH_2CO), 4.48 (8 H, br s, benzyl), 6.99 (8 H, br s, ArH), and 7.12 (8 H, br s, ArH). The molecular ion was not detected by e.i. and f.a.b.-m.s.

N,N-*Ditetradecyl*-N$^{\alpha}$-*t*-*butoxycarbonyl*-N$^{\varepsilon}$-*benzyloxycarbonyl*-L-*lysinamide* (**5**).—Dicyclohexylcarbodi-imide (4.1 g, 20 mmol) was added to a solution of N^{α}-t-butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysine[22] (**4**) (7.3 g, 19 mmol) in dry dichloromethane (40 ml) at 0 °C, and ditetradecylamine (8.0 g, 20 mmol) in dry dichloromethane (20 ml) was added to the mixture after 20 min. The mixture was stirred for 4 h at 0 °C and for a further 17 h at room temperature. The resulting precipitates (*N*,*N*′-dicyclohexylurea) were removed by filtration, the solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (150 ml). The solution was then washed with 10% aqueous citric acid (100 ml × 3), saturated aqueous sodium chloride (100 ml × 3), 4% aqueous sodium hydrogen carbonate (100 ml × 3), and saturated aqueous sodium chloride (100 ml × 3) sequentially. After being dried (Na_2SO_4), the solution was evaporated to dryness under reduced pressure. The residue was chromatographed on a column of silica gel (Wako Gel C-100) with ethyl acetate as eluant. Drying *in vacuo* gave a pale yellow oil (8.5 g, 57%) (Found: C, 72.7; H, 10.7; N, 5.5; M^+ (e.i.) 771. $C_{47}H_{85}N_3O_5$ requires C, 73.1; H, 11.1; N, 5.45%; *M*, 771); R_F (Silica Gel IB of J. T. Baker Chemical Co., New Jersey, U.S.A.; ethyl acetate) 0.87; $\nu_{max.}$(neat) 3 320 (NH), 2 920 and 2 850 (CH), and 1 710 and 1 640 cm^{-1} (C=O); δ_H(400 MHz; $CDCl_3$) 0.88 [6 H, t, *J* 6.8 Hz, $(CH_2)_{13}Me$], 1.25 [48 H, m, $CH_2(CH_2)_{12}Me$], 1.41 [9 H, s, Bu^t], 1.4—1.7 [6 H, m, $CH(CH_2)_3CH_2$], 3.11 [1 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 3.2 [4 H, m, $CH_2(CH_2)_{12}Me$], 3.45 [1 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 4.53 (1 H, m, CH), 4.91 (1 H, m, CH_2NH), 5.08 (2 H, s, benzyl), 5.36 (1 H, d, *J* 10 Hz, NHCH), and 7.35 (5 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 14.1 [$(CH_2)_{13}Me$], 22.4 [$CHCH_2CH_2(CH_2)_2$], 22.6 [$(CH_2)_{12}CH_2Me$], 26.9 [$(CH_2)_2CH_2(CH_2)_{10}Me$], 27.5 [$CH(CH_2)_2CH_2CH_2$], 28.3 [$CMe_3$], 29.3 [$CHCH_2(CH_2)_3$], 29.5 [$(CH_2)_{10}CH_2(CH_2)_2Me$], 29.6 [$(CH_2)_3(CH_2)_7(CH_2)_3Me$], 31.9 [$(CH_2)_{11}CH_2CH_2Me$], 33.7 [$CH_2CH_2(CH_2)_{11}Me$], 40.8 [$CH(CH_2)_3CH_2$], 46.0 and 47.7 [$CH_2(CH_2)_{12}Me$], 49.7 (CH), 66.5 (benzyl), 79.4 [CMe_3], 128.0 (ArC-2 and -4), 128.4 (ArC-3), 136.6 (ArC-1), 155.5 [CO_2CMe_3], 156.4 (CO_2CH_2Ph), and 171.8 (CHCO).

N,N-*Ditetradecyl*-N$^{\varepsilon}$-*benzyloxycarbonyl*-L-*lysinamide* (**6**).—Compound (**5**) (6.4 g, 8.3 mmol) was stirred in 99% formic acid (150 ml) for 4 h at room temperature. After evaporation of the formic acid under reduced pressure, the residue was dissolved in ethyl acetate (150 ml). The solution was then washed with 5% aqueous sodium hydrogen carbonate (100 ml × 3) and saturated aqueous sodium chloride (100 ml × 2). After being dried (Na_2SO_4), the solution was evaporated under reduced pressure. The residue was chromatographed on a column of aluminium oxide (Alumina Activated 300, Nakarai Chemicals) with methanol as eluant. Evaporation of the solvent under reduced pressure gave a pale yellow oil (3.4 g, 61%); R_F(Silica Gel IB; methanol and ethyl acetate) 0.84 and 0.14 respectively; $\nu_{max.}$(neat) 3 350 (NH), 2 920 and 2 850 (CH), and 1 705 and 1 650 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 0.87 [6 H, t, $(CH_2)_{13}Me$], 1.25 (54 H, m, $CH_2(CH_2)_{12}Me$ and $CH(CH_2)_3CH_2$], 2.8—3.5 [6 H, m, $CH_2(CH_2)_{12}Me$ and $CH(CH_2)_3CH_2$]. 4.1—4.5 (1 H, m, CH), 5.00 (2 H, s, benzyl), 5.5—5.9 (1 H, m, NH), 6.3—6.9 (2 H, m, NH_2), and 7.18 (5 H, s, ArH).

When a chloroform solution of the amine was treated with hydrobromic acid, the corresponding hydrobromide salt was obtained quantitatively (Found: C, 66.55; H, 10.35; N, 5.45. $C_{42}H_{77}N_3O_3$·HBr·1/3H_2O requires C, 66.45; H, 10.45; N, 5.55%); δ_H(400 MHz; $CDCl_3$) 0.88 [6 H, t, *J* 6.8 Hz, $(CH_2)_{13}Me$], 1.26 [48 H, m, $CH_2(CH_2)_{12}Me$], 1.53 [6 H, m, $CH(CH_2)_3CH_2$], 3.07 [1 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 3.18 [4 H, m, $CH_2(CH_2)_{12}Me$], 3.52 [1 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 4.45 (1 H, m, CH), 5.08 (2 H, s, benzyl), 5.47 (1 H, m, NH), and 7.33 (5 H, m, ArH).

N,N-*Ditetradecyl*-N$^{\alpha}$-*t*-*butoxycarbonyl*-N$^{\varepsilon}$-*benzyloxycarbonyl*-L-*lysinamide* (**7**).—Triethylamine (2.8 ml, 20 mmol) and (**6**) (2.1 g, 3.1 mmol) were dissolved in dry dichloromethane (20 ml), and the solution was cooled to 0 °C. 6-Bromohexanoyl chloride (3.45 g, 1.62 mmol) in dry dichloromethane (20 ml) was added dropwise to the solution at 0 °C with stirring, and the mixture was stirred further overnight at room temperature. After removal of the insoluble material by filtration, the filtrate was washed with 5% aqueous sodium hydrogen carbonate (100 ml × 2), saturated aqueous sodium chloride (100 ml × 2), 5% aqueous citric acid (100 ml × 2), and saturated aqueous sodium chloride (100 ml × 2) in this sequence. After being dried (Na_2SO_4), the solution was evaporated to dryness under reduced pressure. The crude product was purified by liquid chromatography on a column of silica gel (Wako Gel C-100) with chloroform as eluant and subsequently by gel filtration chromatography on a column of Sephadex LH-20 with methanol as eluant. Evaporation of the solvent under reduced pressure gave a pale yellow viscous oil (2.0 g, 77%) [Found: C, 65.85; H, 9.85; N, 4.55; M^+ (e.i.) 847. $C_{48}H_{86}BrN_3O_4$·3/2H_2O requires C, 65.8; H, 10.25; N, 4.8%; *M* (without 3/2 H_2O) 847]; $\nu_{max.}$(neat) 3 300 (NH), 2 920 and 2 850 (CH), 1 720 and 1 625 (C=O), and 640 cm^{-1} (CBr); δ_H(400 MHz; $CDCl_3$) 0.88 [6 H, t, *J* 6.8 Hz, $(CH_2)_{13}Me$], 1.25 [48 H, m, $CH_2(CH_2)_{12}Me$], 1.4—1.7 [10 H, m, $CH(CH_2)_3CH_2$ and $Br(CH_2)_2(CH_2)_2CH_2$], 1.84 (2 H, m, $BrCH_2CH_2$), 2.20 [2 H, t, *J* 7.6 Hz, $Br(CH_2)_4CH_2$], 3.10 [1 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 3.15—3.35 [4 H, m, $CH_2(CH_2)_{12}Me$], 3.38 (2 H, t, *J* 6.7 Hz, $BrCH_2$), 3.47 [1 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 4.88 (2 H, m, CH and CH_2NH), 5.09 (2 H, s, benzyl), 6.39 (1 H, d, *J* 8.3 Hz, CHNH), and 7.34 (5 H, m, ArH).

N,N-*Ditetradecyl*-N$^{\alpha}$-[6-(*trimethylammonio*)*hexanoyl*]-N$^{\varepsilon}$-*benzyloxycarbonyl*-L-*lysinamide Bromide* (**8**).—Dry trimethylamine gas was introduced into a benzene solution (20 ml) of

compound (**7**) (785 mg, 0.92 mmol) for 3 h at room temperature, and the solution was stirred at the same temperature for 48 h. The benzene was evaporated under reduced pressure and the crude product purified by gel filtration chromatography on a column of Toyopearl HW-40 fine with methanol as eluant. Evaporation of the solvent under reduced pressure gave a pale yellow viscous oil (523 mg, 63%) [Found: C, 65.6; H, 10.4; N, 5.8; $(M - Br)^+$ (f.a.b.) 828. $C_{51}H_{95}BrN_4O_4 \cdot 3/2H_2O$ requires C, 65.5; H, 10.55; N, 5.6%; $M - Br$ (without 3/2 H_2O) 828]; $\nu_{max.}$(neat) 2 920 and 2 850 (CH), and 1 720 and 1 630 cm^{-1} (C=O); δ_H(400 MHz; $CDCl_3$) 0.88 [6 H, t, *J* 6.8 Hz, $(CH_2)_{13}Me$], 1.25 [48 H, m, $CH_2(CH_2)_{12}Me$], 1.3—1.9 [12 H, m, $CH(CH_2)_3CH_2$, and $CH_2(CH_2)_3CH_2N^+$], 2.23 [1 H, m, $CH_2(CH_2)_4N^+$ (non-equivalent)], 2.38 [1 H, m, $CH_2(CH_2)_4N^+$ (non-equivalent)], 3.08 [1 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 3.15—3.35 [4 H, m, $CH_2(CH_2)_{12}Me$], 3.31 [9 H, s, N^+Me_3], 3.46 [3 H, m, $(CH_2)_4CH_2N^+$ and $CH(CH_2)_3CH_2$ (non-equivalent)], 4.74 (1 H, m, CH), 5.08 (2 H, s, benzyl), 5.56 (1 H, m, $NHCH_2$), 7.10 (1 H, br d, CHN*H*), and 7.35 (5 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 14.0 [$(CH_2)_{13}Me$], 22.2 [$CHCH_2CH_2(CH_2)_2$], 22.6 [$(CH_2)_{12}CH_2Me$], 24.6 [$CH_2CH_2(CH_2)_3N^+$], 25.1 [$(CH_2)_2CH_2(CH_2)_2N^+$], 26.9 [$(CH_2)_2CH_2(CH_2)_{10}Me$), 27.5 [$CH(CH_2)_2CH_2CH_2$], 28.8 [$CHCH_2(CH_2)_3$], 29.2 [$(CH_2)_{10}CH_2(CH_2)_2Me$], 29.5 [$(CH_2)_3(CH_2)_7(CH_2)_3Me$], 31.8 [$(CH_2)_{11}CH_2CH_2Me$], 32.2 [$CH_2(CH_2)_4N^+$], 35.2 [$CH_2CH_2(CH_2)_{11}Me$], 38.6 [$(CH_2)_3CH_2CH_2N^+$], 40.4 [$CH(CH_2)_3CH_2$], 46.3 and 47.9 [$CH_2(CH_2)_{12}Me$], 49.1 (CH), 53.2 [$N^+Me_3$], 66.2 [$(CH_2)_4CH_2N^+$], 66.4 (benzyl), 127.9 (ArC-2 and -4), 128.4 (ArC-3), 136.8 (ArC-1), 156.6 (CO_2CH_2Ph), 171.9 (CHCO), and 172.8 (CONHCH).

N,N-*Ditetradecyl*-N$^{\alpha}$-[6-(*trimethylammonio*)*hexanoyl*]-L-*lysinamide Bromide* (**9**).—10% Palladium–carbon (286 mg) was added to compound (**8**) (609 mg, 0.67 mmol) in methanol–acetic acid–water (8:2:1 v/v/v; 15 ml), and hydrogen gas was introduced into the mixture at room temperature for 16 h with stirring. The catalyst was removed by filtration on Celite (Wako No. 545), washed with methanol, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in methanol (1 ml) containing triethylamine (0.2 ml) and chromatographed on a column of Sephadex LH-20 with methanol as eluant. Evaporation of the solvent under reduced pressure gave a colourless viscous oil (370 mg, 71%); R_F(Alumina f of Tokyo Kasei Kogyo Co.; methanol) 0.32; $\nu_{max.}$(neat) 3 400 (NH), 2 920 and 2 850 (CH), and 1 630 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 0.86 [6 H, t, $(CH_2)_{13}Me$], 1.0—2.0 [60 H, m, $CH_2(CH_2)_{12}Me$, $CH(CH_2)_3CH_2$, and $CH_2(CH_2)_3CH_2N^+$], 2.2 [2 H, t, $CH_2(CH_2)_4N^+$], 2.8—3.7 [8 H, m, $CH_2(CH_2)_{12}Me$, $CH(CH_2)_3CH_2$, and $(CH_2)_4CH_2N^+$], 3.30 [9 H, s, N^+Me_3], and 4.5—5.0 (1 H, br, CH).

When a chloroform solution of the amine was treated with hydrobromic acid, the corresponding hydrobromide salt was obtained quantitatively [Found: C, 59.55; H, 10.6; N, 6.2; $(M - HBr - Br)^+$ (f.a.b.) 694. $C_{43}H_{89}BrN_4O_4 \cdot HBr \cdot H_2O$ requires C, 59.15; H, 10.6; N, 6.4%; $M - HBr - Br$ (without H_2O) 694]; δ_H(400 MHz; $CDCl_3$) 0.88 [6 H, t, *J* 6.8 Hz, $(CH_2)_{13}Me$], 1.26 [48 H, m, $CH_2(CH_2)_{12}Me$], 1.35—1.95 [12 H, m, $CH(CH_2)_3CH_2$ and $CH_2(CH_2)_3CH_2N^+$], 2.33 [1 H, m, $CH_2(CH_2)_4N^+$ (non-equivalent)], 2.41 [1 H, m, $CH_2(CH_2)_4N^+$ (non-equivalent)], 3.0—3.3 [8 H, m, $CH_2(CH_2)_{12}Me$, $CH(CH_2)_3CH_2$, and $(CH_2)_4CH_2N^+$], 3.37 [9 H, s, N^+Me_3], 4.74 (1 H, m, CH), and 7.64 (1 H, br d, CHN*H*).

N,N′,N″,N‴-*Tetrakis*[2-(N-{1-(N,N-*ditetradecylcarbamoyl*)-5-[*N*-(*benzyloxycarbonyl*)*aminopentyl*]}*carbamoyl*)*ethyl*]-3,10,21,28-*tetraoxo*-2,11,20,29-*tetra-aza*[3.3.3.3]*paracyclophane* (**10**).—A mixture of $APC(C_2CO_2H)_4$ (201 mg, 0.24 mmol) and thionyl chloride (5 ml, 25 mmol) was stirred for 11 h at room temperature. The excess of thionyl chloride was removed under reduced pressure and a small amount of dry dichloromethane was added to the residue with stirring. The mixture was evaporated under reduced pressure to give the acid chloride. A dichloromethane solution (10 ml) of the acid chloride was added dropwise to a solution of compound (**6**) (1.4 g, 2.1 mmol) and dry triethylamine (1.4 ml, 10 mmol) in dry dichloromethane (20 ml) over 15 min at room temperature, and the mixture was stirred for 5 h at room temperature. After having been evaporated to dryness under reduced pressure, the crude product was purified by gel filtration chromatography on a column of Toyopearl HW-40 fine with methanol–chloroform (1:1 v/v) as eluant. Evaporation of the solvent under reduced pressure gave a pale yellow viscous oil (273 mg, 33%) (Found: C, 73.25; H, 9.85; N, 6.55. $C_{212}H_{344}N_{16}O_{20} \cdot 2H_2O$ requires C, 73.3; H, 10.1; N, 6.45%); $\nu_{max.}$(neat) 2 920 and 2 850 (CH), and 1 710 and 1 620 cm^{-1} (C=O); δ_H(400 MHz; $CDCl_3$) 0.88 [24 H, t, *J* 6.6 Hz, $(CH_2)_{13}Me$], 1.25 [192 H, m, $CH_2(CH_2)_{12}Me$], 1.4—1.95 [24 H, m, $CH(CH_2)_3CH_2$], 2.63 [8 H, m, NCH_2CH_2CO], 3.0—3.6 [24 H, m, $CH_2(CH_2)_{12}Me$ and $CH(CH_2)_3CH_2$], 3.70 (8 H, m, NCH_2CH_2CO), 4.47 (8 H, br s, $PhCH_2N$), 4.86 (8 H, m, CH and CH_2NH), 5.05 (8 H, s, $PhCH_2CO$), 6.76 (4 H, br, CHN*H*), 7.05 (8 H, br s, ArH), and 7.31 (28 H, br s, ArH); δ_C(100 MHz; $CDCl_3$) 14.1 [$(CH_2)_{13}Me$], 22.3 [$CHCH_2CH_2(CH_2)_2$], 22.6 [$(CH_2)_{12}CH_2Me$], 26.8 [$(CH_2)_2CH_2(CH_2)_{10}Me$], 27.5 [$CH(CH_2)_2CH_2CH_2$], 29.3 [$CHCH_2(CH_2)_3$], 29.5 [$(CH_2)_{10}CH_2(CH_2)_2Me$], 29.6 [$(CH_2)_3(CH_2)_7(CH_2)_3Me$], 31.9 [$(CH_2)_{11}CH_2CH_2Me$], 34.1 [$CH_2CH_2(CH_2)_{11}Me$], 35.1 ($NCH_2CH_2CO$), 40.6 [$CH(CH_2)_3CH_2$], 42.0 ($NCH_2CH_2CO$), 46.1 and 47.7 [$CH_2(CH_2)_{12}Me$], 48.7 (CH), 53.1 (C-1, -12, -19, and -30), 66.4 (CO_2CH_2Ph), 127.0 (C-5, -6, -8, -9, -14, -15, -17, -18, -23, -24, -26, -27, -32, -33, -35, and -36), 127.9 (ArC-2 and -4 of CO_2CH_2Ph), 128.4 (ArC-3 of CO_2CH_2Ph), 136.7 (ArC-1 of CO_2CH_2Ph), 137.3 (C-4, -7, -13, -16, -22, -25, -31, and -34), 156.5 (CO_2CH_2Ph), 170.3 (CONH), 171.1 (C-3, -10, -21, and -28), and 171.2 (CHCO).

N,N′,N″,N‴-*Tetrakis*(2-{N-[1-(N,N-*ditetradecylcarbamoyl*)-5-*ammoniopentyl*]*carbamoyl*}*ethyl*)-3,10,21,28-*tetraoxo*-2,11,20,29-*tetra-aza*[3.3.3.3]*paracyclophane Tetrachloride* [$APC(C_2Lys2C_{14})_4$] (**III**).—Dry hydrogen bromide gas was introduced into a mixture of compound (**10**) (153 mg, 0.045 mmol), anisole (1 ml, 9 mmol), and trifluoroacetic acid (25 g, 220 mmol) for 2 h at 0 °C. After evaporation of an excess amount of trifluoroacetic acid under reduced pressure, the residue was purified by gel filtration chromatography on a column of Sephadex LH-20 with methanol–chloroform (1:1 v/v) as eluant. Evaporation of the solvent under reduced pressure gave a pale yellow oil, which was subsequently dissolved in ethanol (3 ml) and applied on a column of Dowex 1-X8 (Cl^-) with ethanol as eluant. Further purification by gel filtration chromatography on a column of Sephadex LH-60 with ethanol as eluant afforded the product as a pale yellow viscous oil (36 mg, 27%) (Found: C, 71.2; H, 10.3; N, 7.15. $C_{180}H_{324}Cl_4N_{16}O_{12}$ requires C, 70.95; H, 10.7; N, 7.35%); $\nu_{max.}$(neat) 2 920 and 2 850 (CH), and 1 620 cm^{-1} (C=O); δ_H(400 MHz; $CDCl_3$) 0.88 [24 H, t, *J* 6.4 Hz, $(CH_2)_{13}Me$], 1.25 [192 H, m, $CH_2(CH_2)_{12}Me$], 1.35—1.9 [24 H, m, $CH(CH_2)_3CH_2$], 2.65 [8 H, m, NCH_2CH_2CO], 3.09 [4 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 3.25 [8 H, m, $CH_2(CH_2)_{12}Me$], 3.50 [4 H, m, $CH(CH_2)_3CH_2$ (non-equivalent)], 3.68 (8 H, m, NCH_2CH_2CO), 4.50 (8 H, br s, $PhCH_2N$), 4.83 (8 H, m, CH and CHN*H*), 7.08 (8 H, br s, ArH), and 7.30 (8 H, br s, ArH); δ_C(100 MHz; $CDCl_3$) 14.1 [$(CH_2)_{13}Me$], 22.3 [$CHCH_2CH_2(CH_2)_2$], 22.6 [$(CH_2)_{12}CH_2Me$], 26.8 [$(CH_2)_2CH_2(CH_2)_{10}Me$], 27.5 [$CH(CH_2)_2CH_2CH_2$], 29.3 [$CHCH_2(CH_2)_3$ and $(CH_2)_{10}CH_2(CH_2)_2Me$], 29.6 [$(CH_2)_3(CH_2)_7(CH_2)_3Me$], 31.9 [$(CH_2)_{11}CH_2CH_2Me$], 33.9

$[CH_2CH_2(CH_2)_{11}Me]$, 35.1 (NCH_2CH_2CO), 39.2 $[CH(CH_2)_3CH_2]$, 42.0 (NCH_2CH_2CO), 46.8 and 48.1 $[CH_2(CH_2)_{12}Me]$, 49.3 (CH), 53.2 (C-1, -12, -19, and -30), 127.1 (C-5, -6, -8, -9, -14, -15, -17, -18, -23, -24, -26, -27, -32, -33, -35, and -36), 137.1 (C-4, -7, -13, -16, -22, -25, -31, and -34), 170.7 (CONH), 171.5 (C-3, -10, -21, and -28), and 171.8 (CHCO).

N,N′,N″,N‴-*Tetrakis*[2-(N-{1-(N,N-*ditetradecylcarbamoyl*)-1-[5-(*trimethylammonio*)*pentanecarboxamido*]*pentan*-5-*yl*}*carbamoyl*)*ethyl*]-3,10,21,28-*tetraoxo*-2,11,20,29-*tetraaza*[3.3.3.3]*paracyclophane Tetrabromide* {APC[C_2Lys(C_5N^+)$2C_{14}$]$_4$} (**IV**).—A mixture of APC(C_2CO_2H)$_4$ (42 mg, 0.051 mmol) and thionyl chloride (5 ml, 25 mmol) was stirred for 14 h at room temperature. The excess of thionyl chloride was evaporated under reduced pressure and a small amount of dry dichloromethane added to the residue with stirring. The mixture was evaporated under reduced pressure to give the acid chloride. A dichloromethane solution (15 ml) of the acid chloride was added dropwise to a solution of compound (**9**) (311 mg, 0.40 mmol) and dry triethylamine (0.2 ml, 1.4 mmol) in dry dichloromethane (20 ml) over 15 min at room temperature, and the mixture stirred for 48 h at room temperature. The mixture was evaporated to dryness under reduced pressure and the crude product purified by gel filtration chromatography on a column of Sephadex LH-20 with methanol as eluant. Evaporation of the solvent under reduced pressure gave a colourless solid (40 mg, 20%), m.p. 144—146 °C (Found: C, 67.65; H, 10.35; N, 6.95. $C_{216}H_{392}Br_4N_{12}O_{16}$ requires C, 67.45; H, 10.3; N, 7.3%); $\nu_{max.}$(KBr disc) 2 920 and 2 850 (CH), and 1 630 cm^{-1} (C=O); δ_H(400 MHz; $CDCl_3$) 0.88 [24 H, t, *J* 6.4 Hz, $(CH_2)_{13}Me$], 1.25 [192 H, m, $CH_2(CH_2)_{12}Me$], 1.35—1.9 [48 H, m, $CH(CH_2)_3CH_2$ and $CH_2(CH_2)_3CH_2N^+$], 2.38 [8 H, m, $CH_2(CH_2)_4N^+$], 2.67 [8 H, m, NCH_2CH_2CO], 2.95—3.6 [32 H, m, $(CH_2)_4CH_2N^+$, $CH_2(CH_2)_{12}Me$, and $CH(CH_2)_3CH_2$], 3.25 [36 H, s, N^+Me_3], 3.69 (8 H, m, NCH_2CH_2CO), 4.53 (8 H, br s, $PhCH_2N$), 4.69 (12 H, m, CH and NH), 7.11 (8 H, br s, ArH), and 7.40 (8 H, br s, ArH); δ_C(100 MHz; $CDCl_3$) 14.0 $[(CH_2)_{13}Me]$, 22.1 $[CHCH_2CH_2(CH_2)_2]$, 22.6 $[(CH_2)_{12}CH_2Me]$, 24.7 $[CH_2CH_2(CH_2)_3N^+]$, 25.1 $[(CH_2)_2CH_2(CH_2)_2N^+]$, 26.9 $[(CH_2)_2CH_2(CH_2)_{10}Me]$, 27.6 $[CH(CH_2)_2CH_2CH_2]$, 28.6 $[CHCH_2(CH_2)_3]$, 29.3 $[(CH_2)_{10}CH_2(CH_2)_2Me]$, 29.6 $[(CH_2)_3(CH_2)_7(CH_2)_3Me]$, 31.8 $[(CH_2)_{11}CH_2CH_2Me]$, 32.0 $[CH_2(CH_2)_4N^+]$, 35.0 $[CH_2CH_2(CH_2)_{11}Me$ and $NCH_2CH_2CO]$, 38.5 $[(CH_2)_3CH_2CH_2N^+]$, 42.0 $[CH(CH_2)_3CH_2$ and $NCH_2CH_2CO]$, 46.4 and 47.9 $[CH_2(CH_2)_{12}Me]$, 49.3 (CH), 53.1 $[N^+Me_3$, C-1, -12, -19, and -30], 66.4 $[(CH_2)_4CH_2N^+]$, 127.0 (C-5, -6, -8, -9, -14, -15, -17, -18, -23, -24, -26, -27, -32, -33, -35, and -36), 137.4 (C-4, -7, -13, -16, -22, -25, -31, and -34), 170.6 ($CONHCH_2$), 171.4 (C-3, -10, -21, and -28), 171.9 (CHCO), and 173.1 (CONHCH).

General Measurements.—Elemental analyses were performed at the Microanalysis Center of Kyushu University. ^1H and ^{13}C N.m.r. spectra were taken on a Hitachi R-24B spectrometer (60 MHz for ^1H) and a JEOL JNM-GX400 spectrometer (400 and 100 MHz for ^1H and ^{13}C, respectively). I.r. spectra were recorded on a JASCO IR-810 spectrophotometer. Mass spectral measurements were carried out with a JEOL JMS-01SG-2 spectrometer (electron impact ionization) and a JEOL JMS-DX300 spectrometer (fast atom bombardment ionization). M.p.s were measured with a Yanagimoto MP-S1 and a Yanaco MP-500D apparatus (hot-plate type). Molecular weight measurements were carried out with a Hitachi Perkin-Elmer 115 vapour pressure osmometer. Surface tension measurements were performed at room temperature with a Shimadzu ST-1 surface tensometer assembled by the Wilhelmy principle. A Beckman Φ71 pH meter equipped with a Beckman 39505 combined electrode was used for pH measurements after calibration with a combination of appropriate aqueous standard buffers. Fluorescence and electronic absorption spectra were recorded on a Hitachi 650-40 fluorescence spectrophotometer and a Hitachi 220A spectrophotometer, respectively. Fluorescence polarization data were recorded on a Union Giken FS-501A spectrophotometer equipped with a Sord M200 Mark II microcomputer. The fluorescence polarization (*P*) was calculated by equation (i), where *I* is the fluorescence intensity,

$$P = (I_{vv} - C_f I_{vh})/(I_{vv} + C_f I_{vh}) \quad \text{(i)}$$

and the subscripts v and h refer to the orientations, vertical and horizontal, respectively, for the excitation and analyser polarizers in this sequence. C_f is the grating correction factor, given by I_{hv}/I_{hh}. The *P* value is alternatively given by equation (ii), where τ is the fluorescence lifetime of a probe, ρ is the

$$1/P - 1/3 = (1/P_0 - 1/3)(1 + 3\tau/\rho) \quad \text{(ii)}$$

relaxation time for rotation of a probe, and P_0 refers to the maximal value of *P* for a probe without any rotational motion.[17] H.p.l.c. analyses were carried out with a Hitachi 635 liquid chromatograph.

Evaluation of Binding Constants.—The substrate binding behaviour of the azacyclophanes was examined by electronic absorption and fluorescence spectroscopy in the following aqueous buffers (0.01 mol dm^{-3}, μ 0.10 with KCl) containing 0—5% (v/v) organic solvent at 30 °C: 2-morpholinoethanesulphonate (MES) and 2-[4-(2-hydroxyethyl)piperazinyl]ethanesulphonate (HEPES) at pH 6.0 and 8.0, respectively. In general, electronic spectra of the guest molecules were measured by changing concentrations of the host molecules. Binding constants for formation of inclusion complexes of the host with various guest molecules at the 1:1 molar ratio (K_1) were calculated on the basis of the Benesi-Hildebrand type relationship[10] (equations (iii) and (iv) for electronic absorption and

$$1/\Delta A = 1/(\Delta\varepsilon[G]_0) + 1/(\Delta\varepsilon K_1[G]_0[H]_0) \quad \text{(iii)}$$

$$1/\Delta I = 1/(\Delta I_c[G]_0) + 1/(\Delta I_c K_1[G]_0[H]_0) \quad \text{(iv)}$$

fluorescence spectroscopy, respectively). Here, ΔA is the absorbance change upon addition of the host, $\Delta\varepsilon$ stands for the difference in molar extinction coefficient between the bound and free guest molecules, ΔI is the extent of fluorescence intensity change upon addition of the host, ΔI_c refers to the difference in fluorescence intensity between the bound and free guest molecules, and $[G]_0$ and $[H]_0$ are the total concentrations of the guest and host molecules, respectively. Good linear correlations of $1/\Delta A$ (or $1/\Delta I$) *vs.* $1/[H]_0$ were obtained for all the measurements, except for pyrene as a guest molecule.

The host–guest interaction between APC[C_2Lys(C_5N^+)-$2C_{14}$]$_4$ and pyrene was analysed according to the following equilibria, equations (v) and (vi), where H·G and H·G·G denote

$$H + G \underset{}{\overset{K_1}{\rightleftharpoons}} H{\cdot}G \quad \text{(v)}$$

$$H{\cdot}G + G \underset{}{\overset{K_2}{\rightleftharpoons}} H{\cdot}G{\cdot}G \quad \text{(vi)}$$

$$K_1 = [H{\cdot}G]/([H][G]) \quad \text{(vii)}$$

$$K_2 = [H{\cdot}G{\cdot}G]/([H{\cdot}G][G]) \quad \text{(viii)}$$

the inclusion complexes of the host (H) with the guest (G) at the molar ratios of 1:1 and 1:2, respectively, and K_1 and K_2 are the respective binding constants defined by equations (vii) and (viii).

The material balances for the host and guest molecules are given by equations (ix) and (x), respectively.

$$[H]_0 = [H] + [H{\cdot}G] + [H{\cdot}G{\cdot}G] \quad \text{(ix)}$$

$$[G]_0 = [G] + [H{\cdot}G] + 2[H{\cdot}G{\cdot}G] \quad \text{(x)}$$

Combination of equations (vii)—(x) and subsequent rearrangement result in equation (xi).

$$K_2K_2([G]_0 - [H{\cdot}G] - 2[H{\cdot}G{\cdot}G])^2([H]_0 - [H{\cdot}G] - [H{\cdot}G{\cdot}G]) - [H{\cdot}G{\cdot}G] = 0 \quad \text{(xi)}$$

where

$$[H{\cdot}G] = (K_1/2K_2)\{([H{\cdot}G{\cdot}G]^2 - (4K_2/K_1) \times ([H{\cdot}G{\cdot}G] - [H]_0)[H{\cdot}G{\cdot}G])^{\frac{1}{2}} - [H{\cdot}G{\cdot}G]\} \quad \text{(xii)}$$

Thus, for given K_1 and K_2 values, [H], [G], [H·G], and [H·G·G] were calculated on the basis of equations (ix)—(xii). On the other hand, a calculated emission intensity (I_{calc}) at the observed wavelength is given by eqation (xiii), where I_G, I_{HG},

$$I_{calc} = I_G[G] + I_{HG}[H{\cdot}G] + I_{HGG}[H{\cdot}G{\cdot}G] \quad \text{(xiii)}$$

and I_{HGG} indicate the corresponding emission intensities per mole for G, H·G, and H·G·G species, respectively. Since the I_G value can be obtained experimentally, the I_{calc} value can be obtained from equation (xiii) for given I_{HG} and I_{HGG} values. Accordingly, computer simulation was carried out to minimize the sum of squares of errors [U; equation (xiv)], where I_{obs} represents the observed emission intensity.

$$U = \sum_{[H]_0} (I_{calc} - I_{obs})^2 \quad \text{(xiv)}$$

Kinetic Measurements.—The photochemical reaction of 2-azidobiphenyl to give carbazole was monitored spectrophotometrically. A solution of 2-azidobiphenyl (5.0×10^{-5} mol dm^{-3}), pyrene (0—5.0×10^{-5} mol dm^{-3}), and APC[C_2Lys(C_5N^+)$2C_{14}$]$_4$ (0—1.0×10^{-4} mol dm^{-3}) in water–ethanol (96:4 or 50:50 v/v) was prepared in a spectrophotometric cell of 1.0 cm path length and deoxygenated with nitrogen stream for 30 min. Each solution was irradiated at 20 ± 1 °C with a JEOL JES-UV-1 UV irradiation unit equipped with a 100 W high pressure mercury lamp (Toshiba SHL-100UV) from a distance of 12 cm. Clear spectral changes, showing isobestic points, were observed by inserting a Toshiba UV-35 cut-filter between the cell and the light source for all kinetic runs. The reaction rate was evaluated from the intensity change in the 290 nm range originating from carbazole. Quantitative formation of carbazole in each kinetic solution after the photolysis was confirmed by h.p.l.c. analysis on a column of Hitachi Gel 3010 with hexane–ether (9:1 v/v) as eluant.

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